Dr. David Kriebel's Preliminary Comments

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

While the toxicologic review is generally well-written, it fails to make clear the relevance of the extensive literature on the health effects of asbestos fibers generally, and other amphibole fibers specifically. Without explicit evidence to the contrary, I assume that the mechanisms of toxicity and quantitative risk relations are similar for Libby Amphibole asbestos and other asbestos fibers. The document suffers from a failure to make this point clearly. It also does not compare the final proposed IUR and RfC with those for other types of asbestos.

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

Zeka A, Gore R, Kriebel D. The two-stage clonal expansion model in occupational cancer epidemiology: results from three cohort studies. Occupational and Environmental Medicine 2011; 68:618-24.

II. Hazard Identification of Libby Amphibole Asbestos

A. Noncancer Health Effects:

1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported **(yes)** and clearly described **(yes)**. If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice **(No)**.

2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described **(yes)**. If a different health endpoint is recommended **(No)** as the critical effect for deriving the RfC, please

identify this effect and provide scientific support for this choice.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described and appropriately conducted? **(yes)** Are the results of these analyses appropriately considered in the RfC derivation? **(yes)** Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the panel have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?

6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) **(yes)** and clearly described? **(yes)** If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

This is an example of a place where experience with other amphibole fibers should have been included. Ignoring this literature leaves the impression that Libby amphibole fibers are assumed to be different, while the appropriate assumption is that they are the same unless specific evidence suggests otherwise. No such evidence has been convincingly presented.

7. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC and whether this information is presented in a transparent manner.

See comment immediately above on other types of amphibole fibers.

B. Inhalation Unit Risk (IUR):

1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted **(Yes)** and clearly described? **(Yes)** If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.

The discussion of the results of the Richardson method should make it clear that the direction of the association between exposure and COPD was negative – suggesting that if proper control for confounding by smoking was possible, it might actually strengthen the asbestos – lung cancer association.

4. Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

I don't think the method was explained clearly in the document. A summary of where the adjustment factors come from should be included, so the reader doesn't need to refer to the original journal article.

Additional specific comments:

p. 4-20, section 4.1.1.3.4. Evidence of carcinogenicity from other studies of amphibole asbestos should be cited here. Similarly in section 4.1.1.4. Noncancer Effects, the literature from other studies of workers exposed to amphiboles should be included.

p. 4-27, line 20. I don't understand the sentence: "Because Larson et al. (2010b) analyzed multiple causes of death, the observed association between exposure and cardiovascular disease-related mortality may reflect, at least in part, a consequence of an underlying respiratory disease."

p. 4-71, line 25. In section 4.5.1.1. Pulmonary Fibrosis (Asbestosis), evidence from other studies of amphiboles should have been included.

p. 4-80, 4.6.2. Mode-of-Action Information. A great deal is known about the mode of action of asbestos fibers generally and amphiboles specifically, which should be assumed to be relevant to Libby asbestos. The mathematical modeling of mesothelioma and lung cancer patterns that has been done for other asbestos exposures shows clearly that cumulative exposure is not the best exposure metric. The duration of exposure is a stronger predictor than the intensity. This is reasonable for an early stage carcinogen, which asbestos appears to be. See work from the 1980s of Peto, Moolgavkar and others. Also the recent Zeka paper I cited on the first page.

p.5-31, section 5.2.3.3.1. Statistical model evaluation and selection. Explain here why BMI considered a relevant covariate. Line 20. "initial modeling was done using a standard logistic regression model, as is commonly applied in 20 analysis of epidemiological data." This is a poor justification. In fact, modern methods for analysis of cross-sectional data avoid the logistic model because the odds ratio over-estimates the prevalence ratio, which is the correct measure of association. See Spiegelman 2005 and Barros 2003 papers referenced below.

p. 5-53. Section 5.4.2. Choice of Study/Data—with Rationale and Justification. This makes clear that the analysis applies only to Libby asbestos. But it provides no justification for this choice.

p. 5-69, line 19. "The RTW exposure metric in this current assessment is sometimes called the cumulative burden, or the area under the curve". This is confusing. The area under the curve (AUC) is often used to refer to the simple cumulative exposure. Here it is the AUC for the "cumulative cumulative exposure" or something like that. I would not describe the RTW as an AUC.

p. 5-72, line 22. Rothman's discussion of comparing latencies is out of date. Time windows rather than lagging is a more widely accepted approach now. See page 321 in Checkoway's occupational epidemiology textbook, 2nd edition, 2004.

References.

Spiegelman D. Am J Epi 2005; 162(3): 199-200. DOI: 10.1093/aje/kwi188
Barros AJD. BMC Medical Research Methodology 2003; 3:21.